PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Defining and measuring suspicion of sepsis: an analysis of routine data
AUTHORS	Inada-Kim, Matthew; Page, Bethan; Maqsood, Imran; Vincent, Charles

VERSION 1 - REVIEW

REVIEWER	Decio Diament Departamento de Pacientes Graves - CTA-A Hospital Israelita Albert Einstein São Paulo, SP, Brasil
REVIEW RETURNED	12-Nov-2016

GENERAL COMMENTS	The main flaw in this study is case definition. ICD-10 codes embrace many different kinds of diseases. Some of them potentially could result in sepsis, but not necessarily so. This could lead to overestimation of incidence or prevalence of disease. Authors had separate 25 ICD-10 codes responsible for 85% of deaths, suggesting that these codes should be monitored as potential sepsis cases. However, diseases represented by these codes could lead to death by other mechanisms, like respiratory failure or kidney failure. Cause of death should be cross-checked with diagnosed codes in order to verify sepsis probability. These data probably would be contained in the HES database and could be easily accessed.

REVIEWER	Simon Nadel St Mary's Hospital, London, UK
REVIEW RETURNED	15-Nov-2016

GENERAL COMMENTS	This is an excellent attempt to understand the characteristics of patients admitted with a "suspicion of sepsis" in a year period in the Oxford Region. It makes many assumptions, some of which are addressed in the limitations and methods. The consensus reached regarding the coding categorisations leave me with certain questions: Why are certain diagnoses included, such as gallstones, diverticular disease, COPD exacerbations, which may not have an infectious aetiology? Although this is not a great number of patients, it may dilute the dataset with unnecessary inclusions. The inclusions would be subject to question and I note a consensus was drawn up, but to suggest this should be adopted widely calls into question some of the methodology which may not be applicable elsewhere. The other major issue which has not been addressed is the

	contribution of the SOS to the mortality, length of stay and readmission rate. While clearly this cannot be addressed using this retrospective methodology, as stated but he authors, these factors need to be discussed as the assumption is that the infection has a major impact of the outcomes, whereas it is just as likely that co-morbidities were just as important. This needs further discussion. The other issue that I am not clear about is the timing of the diagnosis of SOS. Are these all admission data? If so, there are a large number of patients who develop sepsis while already inpatients. Would the methods described in this paper address this important issue?

REVIEWER	Satish Bhagwanjee University of Washington USA Honorarium received for speaking commitments: Pfizer , Australia
REVIEW RETURNED	23-Nov-2016

GENERAL COMMENTS	Definitions: Despite the recognition of sepsis as an entity for centuries we are still grappling with an accurate definition. Many terms have been used including bacteremia, septicemia, sepsis syndrome and toxic shock. This inhomogeneity has resulted in poor discrimination both in relation to defining severity/consequences of the infective process and acceptable disease classification (ICD). First, the old definition is still the basis for describing Sepsis until the new definition has been validated. The authors should change this reference. Second, ICD-10 has poor discriminating ability in defining Sepsis or its severity. Third, the new definition has no value in identifying patients who are not critically ill. The old definition still has value outside the intensive care unit. Fourth, septicemia which has been used for decades is an outdated concept, should be avoided but is still in routine use. Attributing Diagnoses: a. The authors submit that the diagnoses listed were made on admission (page 7, line 3). It is conceivable that some diagnoses were made by health care workers on admission (e.g. Appendix B. Lobar pneumonia, unspecified), however many of the diagnoses could only be made by administrative coders in retrospect (e.g. Appendix B. Sepsis, unspecified). b. It is unlikely that health care providers were able to determine the primary agent responsible for sepsis on admission because this requires a bacteriological laboratory diagnosis. It is common to diagnose Sepsis on admission but source identification and causative organism commonly occurs later in the course of care. The authors submit that blood cultures, clinical judgement and administrative databases should be used to assess the incidence. This is inaccurate. Laboratory tests have been used; although some tests are sensitive there are no specific markers of Sepsis. Blood cultures notoriously under-diagnose sepsis. Clinical assessment has been the mainstay for the diagnosis of Sepsis. Here again we lack sensitivity and specificity. The value of administrative databases for incidence estimation is questionable. 1. The multitude of categories that must be considered to embrace all septic conditions is prohibitive and produces error. 2.Conversely, A40 Streptococcal sepsis and J13 Streptococcal pneumonia could both be used to define the same condition. 3.ICD 9 uses the term septicemia whilst ICD has converted this term to Sepsis. This translation is not direct.

	4. It is likely that many patients with pneumonia who died actually progressed to septic shock before succumbing to the disease. In this study only 21 patients with septic shock were identified (Appendix B. page 28).5.The association between site of infection and outcome has been established previously (5, 6). In this study (Table 2: Top ten suspicion of sepsis, page 13) the sites of infection with the highest mortality were the lower respiratory tract (1,2,5,6,7,8), urinary tract (3)and the abdomen (10) (with cellulitis (9) being about as common as abdomen). General comments Coding: 1. Appendix B: codes should be correctly labeled e.g. item 1. N390 should be N39.0 2. Page 8, line 16: It is unclear where the septicemia codes A40/41 originate from. They do not appear in Tables or Appendix B. It is therefore impossible to interpret "2577 (4.7%) of admissions had a septicemia code". Table 1 is unhelpful Figure 2 should be redrawn after correcting Table 2. References 2 and 3 are incorrect. References 1. American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference: definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. Crit Care Med. 1992;20(6):864-74. 2. Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA : the journal of the American Medical Association. 2016;315(8):801-10. 3. Xu J, Kochanek KD, Murphy SL, Tejada-Vera B. Deaths: final data for 2007. National vital statistics reports : from the Centers for Disease Control and Prevention, National Center for Health Statistics, National Vital Statistics System. 2010;58(19):1-19. 4. Elixhauser A, Friedman B, Stranges E. Septicemia in U.S. Hospitals, 2009: Statistical Brief #122. Healthcare Cost and Utilization Project (HCUP) Statistical Briefs. Rockville MD2006. 5. Vincent JL, Rello J, Marshall J, Silva E, Anzueto A, Martin CD, et al. International study of the prevalence and outcomes of infection in intensive care units. JAMA : the journal of the American Medical Association. 2009;302(21):2323-9. 6. Kempker JA, Martin GS. The Changing Epidemiology and Definitions of Sepsis. Clinics in chest medicine. 2016;37(2):165-79.

VERSION 1 – AUTHOR RESPONSE

Comment	**Response**
Reviewer 1	
The main flaw in this study is case definition. ICD-10 codes embrace many different kinds of diseases. Some of them potentially could result in sepsis, but not necessarily so. This could lead to overestimation of incidence or prevalence of disease.	This reviewer has misunderstood the purpose of our study. Our introduction explains that national guidelines require the identification of patients with "suspicion of sepsis" (pg. 5); the study measures suspicion of sepsis, rather than sepsis itself. As the reviewer rightly says, some of them could result in sepsis but not necessarily so.

Authors had separate 25 ICD-10 codes responsible for 85% of deaths, suggesting that these codes should be monitored as potential sepsis cases. However, diseases represented by these codes could lead to death by other mechanisms, like respiratory failure or kidney failure. Cause of death should be cross-checked with diagnosed codes in order to verify sepsis probability. These data probably would be contained in the HES database and could be easily accessed.	We agree that patients with suspicion of sepsis may die of causes other than sepsis. We have simply reported the mortality rates of the SOS group. However when patients are admitted with infection and then subsequently die, sepsis is most likely to be the cause. The organ dysfunctions (respiratory and kidney failure) mentioned by the reviewer are highly suggestive of sepsis. The argument for identifying suspicion of sepsis is that it reflects the way patients are clinically managed, patients are diagnosed and treated based on a “suspicion of sepsis”. They are intervened on early to prevent full blown sepsis developing, thereby interrupting the dangerous dysregulated and harmful immune response that may emerge. The reviewer states that cause of death should be cross-checked with codes to verify sepsis probability; this is not easily checked as organ dysfunction codes (NCEPOD, 2015) and codes for septic shock (only 21 in a year in our dataset) are severely under-used in the UK.
Reviewer 2	
This is an excellent attempt to understand the characteristics of patients admitted with a "suspicion of sepsis" in a year period in the Oxford Region.	Thank you.
It makes many assumptions, some of which are addressed in the limitations and methods. The consensus reached regarding the coding categorisations leave me with certain questions: Why are certain diagnoses included, such as gallstones, diverticular disease, COPD exacerbations, which may not have an infectious aetiology? Although this is not a great number of patients, it may dilute the dataset with unnecessary inclusions. The inclusions would be subject to question and I note a consensus	This reviewer has a good point and we have adjusted the data in response to this proposal. The original codes were included as a consensus of clinicians agreed that at least in some cases they could pertain to infection. The reviewer’s response has prompted us to remove some of these codes: codes where the presence of infectious aetiology is possible but contentious were re-examined by clinicians post data analysis.

was drawn up, but to suggest this should be adopted widely calls into question some of the methodology which may not be applicable elsewhere.	Gallstones, diverticular disease and COPD exacerbations without infective descriptors are now excluded. Only Chronic obstructive pulmonary disease with acute lower respiratory infection is included in all of the COPD and emphesyma codes; and only codes with gallstones/diverticular disease with infection/abscess are now included. For example, K573 (Diverticular disease of large intestine without perforation or abscess) and K579 (Diverticular disease of intestine, part unspecified, without perforation or abscess) have been removed; this is because cases of diverticular disease of intestine with bacterial aetiology are likely to be coded as K572 (Diverticular disease of large intestine with perforation and abscess) where there is some form of perforation or abscess. **<u>Codes removed</u>** K57.3 - Diverticular disease of large intestine <u>without</u> perforation or abscess K57.9 - Diverticular disease of intestine, part unspecified, <u>without</u> perforation or abscess K80.5 - Calculus of bile duct <u>without</u> cholangitis or cholecystitis I39 Endocarditis and heart valve disorders in diseases classified elsewhere (incl. I39.0, I39.1, I39.2, I39.3, I39.4, I39.8) I41.0 Myocarditis in bacterial diseases classified elsewhere K57.1 Diverticular disease of small intestine <u>without</u> perforation or abscess K57.5 Diverticular disease of both small and large intestine <u>without</u> perforation or abscess) **This has been corrected in Table 1 and Appendices A and B. The top 10 high risk diagnoses in Table 2 and Figure 1 are unaffected by the removal of these codes.**
The other major issue which has not been addressed is the contribution of the SOS to the	This is a good point. We have added material to the

mortality, length of stay and readmission rate. While clearly this cannot be addressed using this retrospective methodology, as stated but he authors, these factors need to be discussed as the assumption is that the infection has a major impact of the outcomes, whereas it is just as likely that co-morbidities were just as important. This needs further discussion.	discussion section to address this. We propose that more research needs to be done looking at whether the presence of an SOS diagnosis is a major factor in determining outcomes, above and beyond other factors such as comorbidities. Our clinical assumption is that the presence of infection has a major impact but this ought to be tested.
The other issue that I am not clear about is the timing of the diagnosis of SOS. Are these all admission data? If so, there are a large number of patients who develop sepsis while already inpatients. Would the methods described in this paper address this important issue?	Yes this is admission data only. Many of the patients who develop sepsis during their stay will have had an infection on admission and therefore be captured by our SOS group. However this methodology does not include patients who develop an infection during their hospital stay and then go onto develop sepsis. We have further clarified this in the discussion section (pg. 10).
Reviewer 3	
Definitions: Despite the recognition of sepsis as an entity for centuries we are still grappling with an accurate definition. Many terms have been used including bacteremia, septicemia, sepsis syndrome and toxic shock. This inhomogeneity has resulted in poor discrimination both in relation to defining severity/consequences of the infective process and acceptable disease classification (ICD). First, the old definition is still the basis for describing Sepsis until the new definition has been validated. The authors should change this reference. Second, ICD-10 has poor discriminating ability in defining Sepsis or its severity. Third, the new definition has no value in identifying patients who are not critically ill. The old definition still has value outside the intensive care unit. Fourth, septicemia which has been used for decades is an outdated concept, should be avoided but is still in routine use.	There has been many changes to definitions of sepsis and no agreed methodology for measuring it as this reviewer rightly states and we discuss in our paper. This study however measures suspicion of sepsis, not sepsis: suspicion of sepsis we argue can be easily measured unlike sepsis, where there is no agreement on how best to measure it. We cite the recent consensus definition for sepsis “life-threatening organ dysfunction caused by a dysregulated host response to infection” (Singer et al., 2016); this is a general definition reached through international consensus which closely matches everyday clinical language and is agreed upon by many experts (Vincent, Martin & Levy, 2016). We do not believe this reference should be changed as it represent current international consensus. We wonder whether the reviewer is referring to qSOFA; qSOFA is an early warning tool proposed in the international consensus paper (Singer et al., 2016) which is yet to be validated and is not a replacement for the old definition (SIRS) (Vincent,

	Martin & Levy, 2016).
Attributing Diagnoses: a. The authors submit that the diagnoses listed were made on admission (page 7, line 3). It is conceivable that some diagnoses were made by health care workers on admission (e.g. Appendix B. Lobar pneumonia, unspecified), however many of the diagnoses could only be made by administrative coders in retrospect (e.g. Appendix B. Sepsis, unspecified). b. It is unlikely that health care providers were able to determine the primary agent responsible for sepsis on admission because this requires a bacteriological laboratory diagnosis. It is common to diagnose Sepsis on admission but source identification and causative organism commonly occurs later in the course of care.	Thank you for pointing out this potential misunderstanding of the coding process. We have added some text to the manuscript explaining how coding works in the UK (pg. 7): coders retrospectively use all information they have access to from patient notes to determine primary reason for admission. This also includes documented positive blood culture results etc.
The authors submit that blood cultures, clinical judgement and administrative databases should be used to assess the incidence. This is inaccurate. Laboratory tests have been used; although some tests are sensitive there are no specific markers of Sepsis. Blood cultures notoriously under-diagnose sepsis. Clinical assessment has been the mainstay for the diagnosis of Sepsis. Here again we lack sensitivity and specificity. The value of administrative databases for incidence estimation is questionable. 1. The multitude of categories that must be considered to embrace all septic conditions is prohibitive and produces error.	As the reviewer says, there are various limitations to methods for measuring the incidence of sepsis, as we discuss in the introduction; there is no “gold standard” test for sepsis (Rhee et al., 2014). When “expert clinical assessment” has been analysed there is wide variation in interpretation (Rhee et al. 2016). Our study measures suspicion of sepsis, not sepsis. Administrative databases represent a pragmatic and effectives means of obtaining suspicion of sepsis outcome data.
2.Conversely, A40 Streptococcal sepsis and J13 Streptococcal pneumonia could both be used to define the same condition.	We only count the primary code at admission; therefore there is not a problem of double counting somebody coded with A40 Streptococcal sepsis for example as a primary code and J13 Streptococcal pneumonia as secondary code.
3.ICD 9 uses the term septicemia whilst ICD has converted this term to Sepsis. This translation is not direct.	Code A41.9 covers sepsis, septicaemia and septic shock.
4. It is likely that many patients with pneumonia who died actually progressed to septic shock before succumbing to the disease. In this study only 21 patients with septic shock were identified (Appendix B. page 28).	As noted by the reviewer, septic shock is under-coded in the UK. As stated in paragraph 4 of the introduction, coders in the UK prioritise documenting the source of infection, e.g. pneumonia and tend not to code sepsis/septic shock (NCEPOD, 2015). This is one the reasons we

	should measure suspicion of sepsis and not sepsis.
The association between site of infection and outcome has been established previously (5, 6). In this study (Table 2: Top ten suspicion of sepsis, page 13) the sites of infection with the highest mortality were the lower respiratory tract (1,2,5,6,7,8), urinary tract (3)and the abdomen (10) (with cellulitis (9) being about as common as abdomen).	The reviewer cites papers which focused on the source of infection in confirmed sepsis cases in intensive care units. Our paper is different as it looks at suspicion of sepsis upon admission to hospital, i.e. the whole hospital population.
Appendix B: codes should be correctly labeled e.g. item 1. N390 should be N39.0	We agree, we have corrected this in all tables.
Page 8, line 16: It is unclear where the septicemia codes A40/41 originate from. They do not appear in Tables or Appendix B. It is therefore impossible to interpret “2577 (4.7%) of admissions had a septicemia code”.	Thank you for clarifying this ambiguity. We have made this clearer in the text. Septicaemia or sepsis codes are any codes starting A40 or A41. All A40 codes have an organism associated with them, A41.8 and A41.9 are the only codes where an organism has not been found and sepsis is suspected. This wasn’t very clear in the text so we have made this clearer by referring to “A40/A41” instead as “sepsis codes, i.e. all codes which start A40 or A41, those which have sepsis in the description” (see pg. 6)
Table 1 is unhelpful. Figure 2 should be redrawn after correcting Table 2.	Table 1 provides clinical insight into which infections are the most common on admission to hospital which we believe most clinicians would find important. The reviewer does not state what needs correcting in Table 2 so we are unsure how to respond to this point. We have checked Table 2 and everything is correct.
References 2 and 3 are incorrect.	We thank the reviewer for spotting this. We have corrected the references accordingly.

VERSION 2 – REVIEW

REVIEWER	Decio Diament Centro de Terapia Intensiva - Adultos Departamento de Pacientes Graves Hospital Israelita Albert Einstein São Paulo, Brasil
REVIEW RETURNED	18-Apr-2017

GENERAL COMMENTS	no additional comments

REVIEWER	Simon Nadel St Mary's Hospital, London, UK
REVIEW RETURNED	07-Feb-2017

GENERAL COMMENTS	Thank you I am happy you have addressed my concerns. Nice work!!